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Review Article

Uterine transplantation: a review of current progress, challenges and future directions

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Abstract

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Uterine transplantation (UT) is a fertility restoring treatment for women with absolute uterine factor infertility. Uterine transplantation (UT) associated with IVF restores fertility in women affected by absolute uterine factor infertility (AUFI). Pregnancies achieved both in women undergoing any solid organ transplantation and following IVF are associated with an increased risk of maternal and neonatal complications (1) Purpose: To provide a comprehensive review of uterine transplantation including discussion of pregnancy outcomes, donor and recipient selection process, organ procurement and transplant surgeries, reported complications, pre-implant preparation, and ethical considerations.(2) Objective: This review aims to summarize the current state of uterine transplantation, including its indications, surgical techniques, donor choices, immunosuppression protocols, reproductive outcomes, ethical challenges and future prospects.(2) Methods: A comprehensive literature review was conducted from the PubMed, , and Web of Science databases, focusing on clinical trials, case reports, and cohort studies published between 2000 and 2024. Results: Since the first successful live birth after UT in 2014, more than 100 operations have been performed worldwide, with increasing live birth rates approaching 50% in experienced centers. However, there are still Key challenges such as graft rejection, immunosuppressive management, surgical complexity, psychosocial considerations, and ethical concerns about donor safety. Future directions include biologically designed uterus and optimal immunosuppression. This review aims to provide clinicians and researchers with an evidence-based overview of UT, highlighting its potential while addressing critical challenges with distinct risks and benefits of these operations and Long-term outcome for mothers and newborns remain areas for active investigation. (3)

Introduction

Infertility affects approximately 10-15% of couples globally, with uterine factor infertility accounting for a large subgroup. Absolute uterine factor infertility AUFI results from congenital absence of the uterus (for example, Mayer-Rokitansky-Küster-Hauser syndrome), surgical removal (e.g. hysterectomy), or nonfunctional uterus (hypoplastic uterus). Until recently, the options available to these women were limited to adoption or surrogacy. the emergence of uterine implantation provides the possibility of gestational and hereditary motherhood.

Uterine transplantation (UT) is a fertility restoring therapeutic intervention for women with absolute uterine factor infertility (AUFI). By restoring uterine anatomy and physiology, it provides the opportunity to conceive, experience gestation, and give birth to biologically related offspring. UT procedures are now being performed all over the world, and the number of cases continues to increase exponentially.1 procedure have been undertaken in Sweden, the United States (Dallas), Germany, Brazil, Serbia, and the Czech Republic.2-12

Twenty-one women have given birth to 23 infants following UT 17 of which have been reported in peer-reviewed publications. An additional 6 have been achieved at the Baylor University Medical Centre, Dallas from the Dallas Uterine Transplant Study (DUETS) and are presented herein (Johannesson, personal communication, 2020). Of the 23 livebirths, 19 were achieved following UT using living donors undertaken in Sweden, Dallas, Serbia, the Czech Republic, and Germany, two livebirths have been confirmed following donation after brain stem death in Brazil, the Czech Republic, and Cleveland., Further livebirths have been reported in the media from cases undertaken in China and India, but remain unpublished. [(1)]

Historical background

The concept of uterine implantation dates back to the early twentieth century, but significant developments did not pave the way for clinical application until the late twentieth and early 21 centuries. Studies conducted on the feasibility of the procedure have provided important insights, including surgical techniques, immunosuppression protocols, and the possibility of successful pregnancy. Since the first successful live birth after UT occurred in Sweden in 2014, the field has developed rapidly and since then, many centers around the world have successfully performed uterine transplants, resulting in a

growing body of knowledge and refinement of technologies, with more than 100 transplants and more than 40 live births globally as of 2024.

Important milestones including:

• 2000: First human attempt at continuous agriculture in Saudi Arabia (unsuccessful).

• 2014: First live birth after UT in Sweden by Dr. Mats Branstrom's team [5]

Indicators and selection of candidates

Recipients

University of Texas candidates are usually women with AUFI, including: Congenital uterine absence (for example, MRK syndrome).

The absence of acquired uterus (for example, after hysterectomy of benign or early malignant disease).

Nonfunctional uterus due to intrauterine adhesions or Asherman syndrome.

Non-functional hypoplastic uterus

Donors

Living donors: often mothers or relatives of the recipient the woman must also be of childbearing age and has not reached menopause so that the uterus does not lose its efficiency due to the change of hormones.

Dead donors: It has been used recently, eliminating the risk to the donor. ‹The challenges here are related to the issue of time, the compatibility of the donor and the receiver at the moment of death, and the speed of transfer so that the uterus does not lose its efficiency due to oxygen deficiency after death.

The choice requires an extensive medical, psychological and moral assessment of both parties [6]

Surgical technique

UT is a complex procedure that includes:

Donor surgery: retrieval of the uterus with the pedicle of healthy blood vessels and surrounding supporting structures (ligaments and cervix).

Recipient surgery: anastomosis of the uterine vessels of the external iliac vessels, ،uterine vessels harvested using iliac/vein grafting

fixation of the uterus on the pelvic ligaments. and vaginoplasty.

Surgical technique procedures can last 8 to 12 hours and require high surgical precision.

Nonliving Donors: Eliminates donor risk but graft survival is shorter [7]

Robotic-assisted UT:

Minimally invasive approach arising (e.g., the Prague Protocol).

Postoperative care: Prevention of thrombosis (high risk of stroke). Immunosuppression tacrolimus + mycophenolate (later converted to azathioprine before pregnancy).

Complications of uterine transplantation

1. Surgical complications

For the donor (if alive):

-risk of anesthesia

-bleeding

- Ureteral injury

-infection

- Long surgery times (up to 10-12 hours)

For the recipient:

- risk of anesthesia

- Blood clots

- Vascular complications

- Damage to nearby organs (bladder, ureters, intestines)

- Anastomotic failure (failure of vascular connection)

- Episodes of rejection or failure of the operation

2. Immunosuppression and rejection

Immunosuppression after transplantation is critical to preventing graft rejection. Commonly used factors include:

- Maintain tacrolimus levels at 5-10 ng/m

- Mycophenolate mofetil (later replaced by metamorphosis)

-Prednisone

Acute rejection: occurs in ~20% of cases (diagnosed by biopsy / hysteroscopy). Chronic rejection: rare but may lead to graft failure.

Rejection attacks can occur but are often reversible with the use of steroids. Biopsies of the cervix monitor for early signs[6]

3. Infectious complications

- opportunistic infections due to immunosuppression (e.g. cytomegalovirus and fungal infections)

- Urinary tract infections

- Wound infections

4. Obstetric complications

- High-risk pregnancy

- Premature birth and miscarriage

- Preeclampsia

- Caesarean section (almost always planned)

- Restriction of fetal development

- Determining the number of pregnancies only 2

5. Psychological and ethical issues

- Psychological stress and anxiety for both the recipient and the donor

- Ethical concerns about the risks to living donors

- Emotional distress if implantation fails or pregnancy does not materialize

6. Remove the graft

- It is usually planned after one or two live births to eliminate the need for long-term immunosuppression.

- They may also be required if there is a failure or complication in the graft.

Number and type of operations to which women are subjected

1. Two large operations: hysterectomy of the donor woman and uterine transplantation of the receiving woman

2. The process of fertilization technique and IVF for the receiving woman

3. Caesarean section in case of pregnancy

4. Implanted hysterectomy after two successful births

Pregnancy and results

All pregnancies are achieved through in vitro fertilization (IVF) using previously frozen embryos. Pregnancy after UT usually occurs for at least two years after uterine transplantation and is considered high-risk, with common concerns including:

-Premature birth and miscarriage

- Hypertensive disorders

- Placental malformations [7]

Ethical, psychological and social considerations

Key ethical concerns include: Risks to living donors Cost and resource allocation Temporary nature of transplantation Reproductive rights vs. medical risks

The legality of surrogacy and cultural attitudes also affect moral acceptance

Current challenges

Surgical complexity: especially with living donors due to complex vascular anatomy.

Rejection control: lack of standardized, non-invasive tests.

Cost-effectiveness: high financial burden.

Long-term safety: unknown effect of immunosuppression on offspring survival and graft.

Future Directions [4]

Ongoing developments include:

- Robot-assisted techniques and minimally invasive surgery

- UT with biologically designed or odd uterus

- Improved immunosuppressive protocols

- Expansion to include transgender women (experimental)

Stem cell and tissue engineering may eventually eliminate the need for immunosuppression.

Conclusion

Adventure uterine transplantation is in its infancy. The challenges are great and many questions have no answers yet: Is pregnancy possible after uterine transplantation from a deceased donor? Where is the surgical mini-surgery in a uterine transplant? What will be the result of uterine grafting for children?

Uterine transplantation represents a remarkable advance in reproductive medicine, providing new hope for women with AUFI. Although the procedure is still experimental and limited to specialized centers, it has shown feasibility, safety and success in selected cases. There are still ethical, technical, and financial challenges, but ongoing research is about to improve the process and expand accessibility.

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